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Review

Glaucoma and obstructive sleep apnoea syndrome

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Abstract

Glaucoma is increasingly recognized as a manifestation of both ocular and systemic risk factors. A number of disorders associated with reduced blood flow and ischaemia, collectively termed vascular risk factors, such as migraine, Raynaud's phenomenon, atrial fibrillation and reduced nocturnal blood pressure, lead to decreased ocular perfusion pressure. During sleep, alterations occur in cardiovascular physiology that are balanced by autoregulation to maintain homeostasis. However, in obstructive sleep apnoea (OSA), the normal physiological balance is upset. A potentially modifiable risk factor, OSA has been increasingly associated with glaucoma independent of intraocular pressure. OSA may alter blood flow to the optic nerve head and, in combination with other predisposing factors, lead to decreased ocular perfusion pressure. This in turn may directly affect the optic nerve or it may indirectly increase its susceptibility to other insults. The purpose of this review is to shed light on the association between OSA and glaucoma.

Key words: CPAP, glaucoma, normal-tension glaucoma, sleep apnoea.

Introduction

Glaucoma is a progressive optic neuropathy characterized by a distinctive pattern of optic nerve head and visual field (VF) damage caused by a number of different diseases which affect the eye. Most, but not all, of these diseases are associated with elevated intraocular pressure (IOP), which remains the most important known risk factor for glaucomatous damage, but it is nevertheless only a risk factor, and not the disease itself. Currently, IOP is no longer integral to the definition of glaucoma, which can be better described as an ocular neurodegenerative disorder representing a final common pathway produced by a multiplicity of risk factors and ocular disorders.

Reduction of IOP remains the only consistently modifiable risk factor for slowing or delaying the progression of glaucoma and the only treatment modality which has been consistently proven in clinical trials to be effective. However, VF deterioration still occurs in many patients despite IOP control in the normal and even low normal range. This realization has stimulated the search to identify additional risk factors, including those associated with underlying systemic disorders and those common to neurodegenerative diseases as a whole.

Obstructive sleep apnoea (OSA) or obstructive sleep apnoea syndrome (OSAS) is an underrecognized disorder with important systemic implications. It is characterized by repeated episodes of upper airway obstruction during sleep combined with daytime sleepiness. Upper airway function is influenced by neuromuscular tone, upper airway muscular synchrony and the stage of sleep.[1] Hypotonia of the upper airway musculature occurs more frequently in the rapid-eye-movement (REM) stage of sleep, resulting in airflow obstruction. Upper airway obstruction may be grouped into three categories, which include OSAS, sleep hypopnoea and upper airway resistance syndrome. OSAS is the most severe form of intermittent upper airway obstruction, with more mild forms ranging from

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primary snoring, to upper airway resistance syndrome, to obstructive sleep apnoea. Sleep hypopnoea is not a recognized diagnosis in the United States. Hypopnoeas are events scored on polysomography (PSG) or home sleep study. OSAS consists of complete cessation of airflow, whereas upper airway resistance syndrome is the least severe, consisting of snoring without a significant decrease in airflow.

Some, but not all, apnoeas and hypopnoeas lead to arousals. Upper airway obstruction is exacerbated by a large tongue, small airway, large neck and obesity.[1] The severity of sleep apnoea is defined by strict criteria of nasal airflow, respiratory effort and oxygen saturation, detected on overnight PSG or portable sleep testing monitors. The presence of sleep apnoea is defined as five apnoeas or hypopnoeas per hour during the overnight sleep study. Not all patients with OSA have daytime sleepiness, hence the terminological distinction between OSAS and OSA. In the literature, however, particularly with studies performed by non-sleep specialists, the distinction is blurred, and terminology is used inconsistently. Mild, moderate and severe sleep apnoea are often used in reports, without distinguishing between OSA and OSAS. For this reason, we have chosen to use simply the abbreviation OSAS, realizing that not all patients with sleep apnoea have daytime hypersomnolence.

OSAS influences many facets of physiological function, affecting the pulmonary, cardiovascular and cerebrovascular systems. Associations between OSAS and ocular disease have been well documented. These include glaucoma, non-arteritic ischaemic optic neuropathy (NAION), bilateral disc oedema, floppy eyelid syndrome, blepharitis, ptosis, papillary conjunctivitis, filamentary keratitis, retinal vascular tortuosity and central serous chorioretinopathy.[2] The aim of this review is to provide a better understanding of the relationship between OSAS and glaucoma. We reviewed the literature on OSAS and its association with glaucoma in the context of IOP and IOP-independent risk factors.

Sleep

Sleep plays an integral role in homeostasis. There are two distinct types of sleep, namely REM and non-rapid eye movement (NREM). REM sleep accounts for 20–25% of sleep time and tends to occur more frequently during the second half of the night. It is characterized by REMs, arousal electroencephalography (EEG), atonia and dreaming.[3] NREM predominates earlier in the night and is further divided into three stages relating to the frequency of EEG waveforms. Stage 3 is the deepest form of sleep, constituted by delta waves or low-frequency EEG.[3]

Cardiovascular physiology differs between sleep and wakefulness. During sleep, the overall sympathetic tone normally decreases, resulting in nocturnal blood pressure dips of 10–20%, the typical dip being about 15 mmHg.[4] Ocular perfusion generally remains stable due to the supine position. However, sleep is not uniform but is cyclical, alternating between NREM and REM sleep. Sympathetic activity, heart rate and blood pressure tend to decrease during NREM sleep.[5] REM sleep is further broken down into tonic and phasic cycles. Sympathetic activity decreases in the tonic phase and increases in the phasic period. This makes REM sleep haemodynamically variable.[3] Due to a close relationship between the autonomic system and the cardiovascular system, variations in the sympathetic system will result in fluctuations in blood pressure and heart rate. Autoregulation of blood flow is designed to maintain perfusion to tissues to meet their demands during times of cardiovascular fluctuation. With intact autoregulation, the changes during REM sleep will be counterbalanced to maintain blood flow. When there is autonomic dysregulation, also termed autonomic dysfunction, pathological changes ensue.

OSAS

The recognition and understanding of OSAS has grown steadily over the past few decades. Although underdiagnosed, the most recent estimates suggest that sleep apnoea defined by apnoea-hypopnoea index (AHI) ≥ 5 occurs in about 20% of men and 10% of women.[6] Risk factors predisposing to OSAS include obesity, male gender, upper airway abnormalities, alcohol use, snoring, sedatives and enlarged neck girth.[7] Common symptoms include excessive daytime sleepiness, difficulty concentrating, memory problems, and morning and daytime headaches. Home sleep studies or PSG define the existence and severity of OSAS by calculating the total number of respiratory events per hour (respiratory disturbance index [RDI], or AHI).[7,8]

OSAS has lasting physiological implications that persist beyond sleeping. It was identified as a treatable secondary cause of hypertension by the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[9] OSAS is associated with pulmonary hypertension, myocardial infarction, cardiac arrhythmia, congestive heart failure, stroke, cardiac-related mortality and all-cause mortality.[7,10,11] The Sleep Heart Health Study observed a direct rela-

tionship between the RDI in patients with OSAS and stroke, heart failure and vascular disease.[7] OSAS is also associated with surges in blood pressure, endothelial dysfunction,[12] carotid plaques and coagulation abnormalities.[7,13]

The pathophysiology of OSAS begins with an apnoeic episode or hypopneic episode leading to oxygen desaturation. Apnoeas and/or hypopnoeas can lead to repeated arousals during sleep which in turn cause excessive daytime sleepiness. This leads to a cycle of apnoea and arousal, resulting in poor sleep. A key characteristic of sleep apnoea is that the subject does not remember awakening. Additionally, intermittent hypoxia and arousals can lead to an increase in sympathetic tone.[14] Sympathetic activation causes a myriad of downstream effects. For example, it can activate the renin–angiotensin system, which can lead to an increase in blood pressure.[3,12] In addition to sympathetic activation, hypoxia itself plays a significant role. Hypoxia and sustained increases in blood pressure can damage vascular endothelium, decreasing responsiveness to vasodilators, such as nitric oxide (NO).[15] This leads to autonomic dysfunction or an altered blood flow because of an imbalance of vasodilation and vasoconstriction. Vasoconstrictors, such as endothelin-1, are also increased in OSAS, exacerbating vascular dysregulation.[3,12] Hypoxia and subsequent reperfusion can also lead to oxidative stress and inflammation, evidenced by increased levels of inflammatory markers and reactive oxygen species.[16] These may have numerous detrimental effects on the vascular endothelium.

Ocular conditions

Ocular diseases associated with OSAS include glaucoma, NAION, floppy eyelid syndrome, bilateral disc oedema, blepharitis, ptosis, papillary conjunctivitis, filamentary keratitis, retinal vascular tortuosity and central serous chorioretinopathy. Although there are many hypotheses, it is not precisely clear how each condition relates to OSAS. We will discuss floppy eyelid syndrome, NAION and disc oedema because these are reported more frequently and may be most relevant to the discussion on glaucoma and OSA.

Floppy eyelid syndrome is characterized by easily everted lids in the setting of papillary conjunctivitis. Up to 90–100% of floppy eyelid syndrome patients have OSAS.[17–19] Histological studies show loss of elastin fibres with upregulation of elastolytic proteases in the tarsal plates of the lids, which is thought to be mediated by mechanical stress and/or alternating ischaemic/reperfusion injury.[20,21] Hypoxia and subsequent reperfusion can lead to upregulation of matrix metalloproteinases.[22]

OSAS has also been implicated in NAION. Both Mojon *et al.* and Palombi *et al.* prospectively performed PSG in NAION, observing an OSAS prevalence of 71% (12/17) and 89% (26/27), respectively.[23] Postulated theories included direct anoxic damage to the optic nerve, indirect optic nerve damage through blood pressure variations, ischaemia-reperfusion injury, imbalances between NO and endothelin, and hypercoagulability.[23–25] In addition, bilateral disc oedema and papilloedema were observed in patients with OSAS, and this often responded to continuous positive airway pressure (CPAP).[26,27] Sugita *et al.* performed continuous intracranial pressure monitoring in patients with OSAS and reported increases in intracranial pressure during apnoeic periods which directly correlated to the duration of apnoea and decrease in oxyhaemoglobin saturation.[28] This led to the hypothesis that hypercapnea in OSAS results in increased intracranial pressure, subsequently causing bilateral disc oedema or papilloedema.

Evidence for glaucoma and OSAS

Elevated IOP is a well-established modifiable risk factor for the development and progression of glaucoma.[29–31] Other risk factors include age, family history, race,[32] thinner central cornea,[29–31] worse VF at baseline,[29–31,33] increased cup : disc ratio[29,31] and optic disc haemorrhages.[34] Given that glaucoma progression occurs in some patients despite a very low IOP, potentially modifiable systemic associations, such as OSAS, are particularly relevant.

In 1982, Walsh and Montplaisir[35] first described an association between OSAS and glaucoma in five patients in two generations within the same family. A relatively high prevalence of glaucoma was later observed in patients with OSAS and floppy eyelid syndrome. In one series, 6 of 69 patients (8.7%) with floppy eyelid syndrome had glaucoma.[36] Subsequently, five of six studies observed a significant association between glaucoma and OSAS, ranging from 5.7% to 27% (Table 1).[37–41] The study sizes ranged from 30 to over 200 patients, and all patients had either a prospective PSG (Mojon *et al.*, Lin *et al.*) or were referred for ophthalmic examination directly after a positive PSG for OSAS in a consecutive manner (Sergi *et al.*; Bendel *et al.*; Karakucuk *et al.*). One study using a historical positive PSG observed no association between OSA and glaucoma (2.2% glaucoma in OSA).[42] When the prevalence of OSAS was studied in glaucoma cohorts, four of five studies showed a significant association, ranging from 20–55% (Table 2).[43–46] These reports performed PSG in a prospective fashion but were limited by their small numbers, reporting on 30 or less patients (Table 2). The study without an association by

Table 1. Studies investigating glaucoma prevalence in obstructive sleep apnoea

Reference	Study design	Number studied	Type of patient	PSG	Results	OAG	POAG	NTG	Significant association
Mojon *et al.*[37]	Cross-sectional	114	Referred PSG	Prospective PSG	69 OSA	7.2% (5/69)	4.3% (3/69)	2.9% (2/69)	Yes
Sergi *et al.*[38]	Case control	51 OSA; 40 control	OSA (consecutive) and control	Referred after + PSG	51 OSA 40 Control	5.9% (3/51) 0	0 0	5.9% (3/51) 0	Yes
Bendel *et al.*[40]	Cross-sectional	100	OSA (consecutive)	Referred after + PSG	100 OSA	27% (27/100)	–	–	Yes
Lin *et al.*[39]	Case control	256	Referred PSG	Prospective PSG	209 OSA 38 Control	5.7% (12/209) 0	0 0	5.7% (12/209) 0	Yes
Karakucuk *et al.*[41]	Case control	31 OSA; 25 control	OSA (consecutive) and control	Referred after + PSG	31 OSA 25 Control	12.9% (4/31) 0	3.2% (1/31) 0	9.7% (3/31) 0	Yes
Geyer *et al.*[42]	Cross-sectional	390	OSA	Historical + PSG	228 OSA	2.2% (5/228)	1.3% (3/228)	0.9% (2/228)	No

–, unknown; NTG, normal-tension glaucoma; OAG, open-angle glaucoma; OSA, obstructive sleep apnoea; POAG, primary open-angle glaucoma; PSG, polysomography.

Girkin *et al.*[47] retrospectively used International Statistical Classification of Diseases and Related Health Problems (ICD-9) codes for the diagnosis of OSAS, rather than prospective results from PSG testing, limiting its validity.

Given that OSAS has measurable components, such as RDI and oxygen desaturations, correlation to VF indices and retinal nerve fibre loss are particularly relevant. Two studies showed an association between RDI and VF indices. Mojon *et al.*,[37] in a cross-sectional review, found glaucoma in 5 of 69 patients (7.2%) diagnosed with OSAS by PSG prospectively (RDI $\geq$ 10) from a group of 114 patients with sleep disturbance: three patients had primary open-angle glaucoma (POAG) (4.3%) and two patients had normal-tension glaucoma (NTG) (2.9%). The prevalence of open-angle glaucoma was higher than the expected prevalence of 2% in the Caucasian population.[48] None of the 45 patients without OSAS were diagnosed with glaucoma. The RDI, when controlled for age and body mass index, correlated significantly with untreated IOP, VF loss and the diagnosis of glaucoma. In a similar trial, Sergi *et al.*[38] in 2007 performed prospective PSG and ophthalmic examinations on 51 consecutive OSA patients (RDI $\geq$ 10) and 40 age-matched controls, observing NTG in 5.9% (3/51) *versus* 0% in the control group. A significant correlation was seen between AHI and IOP, mean deviation of VF, cup : disc ratio and various ocular parameters such as the mean retinal nerve fibre layer (RNFL) thickness measured by optical coherence tomography. In a study of OSAS and VF indices, Tsang *et al.*[49] in 41 consecutive moderate to severe OSAS patients (excluding glaucoma patients) found a statistically significant increase in mean deviation and pattern standard deviation (PSD) on prospective ophthalmic examination compared with 35 aged-matched controls.[49]

The severity of OSAS represented by AHI has correlated with that of glaucomatous damage. Similar to the earlier mentioned correlation between AHI and RNFL thickness, Kargi *et al.*[50] in a prospective controlled trial of 34 OSAS patients and 20 age-matched controls (excluding glaucoma patients) showed a significant negative correlation between both OSAS and AHI and RNFL thickness using GDx Nerve Fiber Analyzer (Laser Diagnostic Technologies Inc., San Diego, CA, USA). Lin *et al.*[39] diagnosed NTG in 12 of 209 patients (5.7%) consecutively diagnosed with OSAS by prospective PSG (RDI $\geq$ 5). Eight of 12 patients with NTG had an AHI $\geq$ 15, which may be considered moderate OSA. RNFL, as measured by Stratus optical coherence tomography (Carl Zeiss Meditec Inc., Dublin, CA, USA), was significantly decreased in patients with RDI $\geq$ 15, although the RNFL thickness did not correlate with RDI. The mean saturation of oxgen and the lowest saturation

Table 2. Studies investigating obstructive sleep apnoea prevalence in glaucoma

Reference	Study design	Number studied	PSG	Type of patient completing PSG	Results
Mojon *et al.*[43]	Cross-sectional	30	Prospective	POAG	20% (6/30) OSA
Mojon *et al.*[44]	Cross-sectional	16	Prospective	NTG	43.8% (7/16) OSA
Marcus *et al.*[45]	Case controls	23 NTG; 14 NTG suspect; 30 controls	Prospective	9 NTG + Sleep history	55.5% (5/9) OSA
			Prospective	4 NTG suspect + Sleep history	50% (2/4) OSA
			Prospective	1 Controls + Sleep history	100% (1/1) OSA
Blumen Ohana *et al.*[46]	Cross-sectional	25 POAG; 6 NTG	Prospective	25 POAG + Sleep history	48% (12/25) OSA
			Prospective	6 NTG + Sleep history	50% (3/6) OSA
Girkin *et al.*[47]	Case controls (nested)	667 OAG	Unknown	No known PSG	1.1% (7/667) OSA
		6667 Nested controls	Unknown	No known PSG	0.5% (32/6667) OSA

NTG, normal-tension glaucoma; OAG, open-angle glaucoma; OSA, obstructive sleep apnoea; POAG, primary open-angle glaucoma; PSG, polysomography.

of oxygen did correlate with OSAS. In a follow-up study of 105 OSAS patients (excluding glaucoma patients) compared with 22 age-matched controls, Lin *et al.*[51] showed a significantly thinner RNFL measured by Stratus optical coherence tomography in moderate–severe OSAS compared with mild OSAS and controls. They also showed a significantly thinner RNFL in those patients with lower oxygen saturation, suggesting a hypoxia-mediated optic neuropathy. In another study, Bendel *et al.*[40] diagnosed glaucoma in 27 of 100 consecutive OSA patients who had a PSG within 2 days of ophthalmic examination (RDI $\geq$ 15). However, they did not find a correlation between RDI and glaucoma.

Sergi *et al.*[38] also performed visual evoked potentials (VEP) and pattern electroretinography (PERG) on their 51 OSAS patients and 40 matched controls, showing an abnormal VEP in 45% (23 patients) and abnormal PERG in 37% (19 patients) in the OSAS group, whereas VEP and PERG were all normal in the control group. Both AHI and IOP were significantly greater in those patients with abnormal VEP and PERG, and all three patients with NTG had pathological VEP, PERG and RNFL thickness. These data suggest that the apnoeic periods may damage retinal ganglion cells (RGC) and their axons. Although hypoxia is sometimes felt to be the culprit, in this study, there was no significant association between oxyhaemoglobin saturation and the time saturation was below 90% to ophthalmic variables.

When evaluating glaucoma cohorts for OSAS, four of five studies showed a significant association (Table 2). Mojon *et al.*[43] performed PSG on 30 consecutive POAG patients and matched them to published historical controls observing 20% OSAS in glaucoma patients (6/30) *versus* 11% OSAS in historical controls, which was significant. In a similar study, these same authors observed OSAS in 7 of 16 NTG patients (44%).[44] Blumen Ohana *et al.*[46] reported OSAS in 50% of NTG patients (3/6) and 48% of open-angle glaucoma (OAG) patients (12/25). And similarly, Marcus *et al.*[45] reported OSAS in 55.5% of NTG patients (5/9) and in 50% of NTG suspects patients (2/4). The major limitation of all these studies was their limited number of patients. One study performed with questionnaires reported a greater increase in snoring, insomnia and excessive daytime sleepiness in POAG patients.[52]

Five studies have suggested that there is not a significant association between OSAS and glaucoma. Geyer *et al.*[42] conducted a cross-sectional study on 228 patients with OSAS, showing POAG in 5 out of 228 patients for a prevalence of 2%, which overlaps within the expected prevalence for Caucasians (1.7–3%). The major limitation of the study included a time lapse between the PSG and ophthalmic examination, as patients were recalled based on prior OSAS diagnosis. Presumably, some of these patients received CPAP therapy, which has been reported to improve glaucoma in OSAS patients.[53,54] Roberts *et al.*[55] found no statistically significant association between glaucoma and either nocturnal oxygen desaturation or sleep-disordered breathing. Another small study in Thailand found no association.[56]

In a study by Girkin *et al.*,[47] there was no significant association seen between OSAS and glaucoma in 667 cases of glaucoma compared with 6667 nested controls. There were seven cases of OSAS in 667 patients (1.1%) compared with 32 in the control group (0.5%). This study, although large, determined both glaucoma and OSAS through ICD-9 codes without known PSG, which introduces error of miscoding and misdiagnosis. With the use of nested controls, the authors noted that this may bias the study towards the null hypothesis. In addition, there was not a clear way for the investigators to know if the patients were receiving care for their OSAS.

A recent far larger database study has also suggested a lack of association between both high-tension glaucoma and NTG and OSAS.[57] In this retrospective analysis of over 2 million patients belonging to a medical plan, over 156 000 (6.9%) had a diagnosis of sleep apnoea. The authors found that there was no difference of having high-tension glaucoma or NTG between individuals without sleep apnoea or with sleep apnoea, irrespective of treatment with CPAP after adjustment for confounding factors. There was a significantly increased hazard of NAION, papilloedema and idiopathic intracranial hypertension among individuals with sleep apnoea. Limitations, including the lack of associated ophthalmic information and severity of sleep apnoea, are discussed.[57]

Glaucoma risk factors

IOP in glaucoma and OSAS

The relationship described earlier between OSAS and glaucoma may be dependent upon IOP or IOP-independent risk factors. IOP in both normal and glaucoma patients tends to peak nocturnally,[58–60] and this rise thus ordinarily remains undiscovered or unmeasured in the preponderance of patients, leading to IOP-dependent glaucomatous damage.[58,60] IOP is determined by the level of aqueous humour formation, resistance at the outflow tracts and episcleral venous pressure. Although aqueous humour formation decreases at night,[61] the IOP increases due to an increase in episcleral venous pressure in the supine position.[62] Other factors that may influence IOP at night are the haemodynamic system, autonomic nervous system and stage of sleep.[63]

OSAS has the potential to affect these factors through an increase in blood pressure, increase in sympathetic tone and through changes in sleep architecture. Three studies listed earlier on glaucoma prevalence in OSAS reported a significant association between AHI and IOP.[37,38,41] However, the physiological changes seen in OSAS do not necessarily elevate IOP. For example, an increase in systolic blood pressure can increase the IOP, but even large increases in blood pressure of 10 mmHg may elevate IOP negligibly by 0.23–0.44 mmHg.[64] Additionally, a large longitudinal study reported hypertension to protect against glaucoma (The Barbados Eye Studies [BESs]).[32] Normally, IOP is highest during slow-wave sleep and lowest during REM sleep.[63] OSAS tends to decrease the amount of time spent in slow-wave sleep, theoretically producing a lower IOP. Restoration of normal breathing patterns with CPAP therapy elevated IOP to a normal pattern in 12 patients.[63] Pepin *et al*. reported re-establishment of normal IOP and blood pressure rhythm with CPAP, citing a likely positive effect on glaucoma treatment due to improvements in other underlying vascular variables.[63] Additionally, simulated increased inspiratory effort against a closed glottis (Muller's manoeuvre) as in OSAS, causes a dose-dependent decrease in IOP.[65] Increased inspiratory effort creates a negative thoracic pressure, which increases venous return, theoretically lowering episcleral venous pressure (EVP) and resulting in a lowered IOP. However, Goldblum *et al*.[66] found no changes in IOP after prolonged apnoea in patients with NTG and OSAS compared with controls. Given these reports, the contribution of IOP to glaucomatous damage in OSAS is likely minimal.

Vascular system in glaucoma and OSAS

Ocular perfusion pressure

The role of ocular blood flow and ischaemia in glaucoma is not clear. A classic early series nearly 40 years ago of 29 NTG patients consisted of 10 patients with a history of haemodynamic shock, prompting an interest in nocturnal hypotension and glaucoma.[67] Further interest in the role of the cardiovascular system to the development or progression of glaucoma was stimulated by the presence of progression despite a low IOP, and associations between vascular disorders and glaucoma such as migraine headaches and atrial fibrillation. Newer epidemiological reports have associated low nocturnal ocular perfusion pressure (blood pressure minus IOP) and glaucoma. The Baltimore Eye Study, Egna-Neumarkt Study, Rotterdam Eye Study and BESs reported an increased risk of OAG with a low diastolic perfusion pressure.[68] The Early Manifest Glaucoma Trial revealed a higher risk of glaucoma progression with a lower systolic blood pressure and a lower systolic ocular perfusion pressure, and the BESs observed a 9% decrease risk of OAG with an increase of 10 mmHg in systolic blood pressure.[30,32] These findings suggest that high blood pressure may protect against glaucoma, whereas low ocular perfusion pressure may promote its development.[30,32,64] Although OSAS does not commonly result in a decrease of ocular perfusion pressure, the association of glaucoma with a lowered perfusion pressure opens the door to other vascular aetiological concepts.

At night, normally, the sympathetic output decreases, resulting in blood pressure dips by 10–20%, with a typical nocturnal dip of 15 mmHg.[4] Ocular perfusion pressure generally remains stable, because blood pressure around the eye increases in the supine position. Ten percent of people are 'non-dippers' which may result in part from autonomic dysfunction, steroid use, high activity level, renal

disease, postmenopause or poor sleep quality.[4] Non-dippers are at increased risk for cardiovascular abnormalities, whereas extreme dippers (>20% dip in blood pressure), in contrast, have less cardiovascular morbidities as they are protected from hypertension-related end-organ damage at night.[4] Extreme dipping, though, has been associated with glaucoma progression. Graham and Drance[69] showed greater progression of glaucoma damage in patients who had larger dips in blood pressure. On the other hand, in a study of NTG and age-matched controls, there was no difference in nocturnal dipping, but the NTG patients had greater nocturnal variation in blood pressure.[70] Two other studies reported that both extreme dippers and non-dippers were more likely to progress, suggesting autonomic dysfunction in these patients.[71,72] Other reports found a smaller dip in blood pressure in glaucoma patients who progressed *versus* those who did not.[73,74]

The relationship between nocturnal blood pressure, glaucoma and OSAS is complex and incompletely understood. Through elevated blood pressure and sympathetic tone, OSAS can cause damage to vascular endothelium. This in turn leads to endothelial dysfunction, which can cause non-dipping of blood pressure at night.[75,76] Endothelial dysregulation can alter blood flow at and around the optic nerve head, potentially lowering ocular perfusion and increasing the risk for glaucoma.[4]

Autonomic dysfunction

Experimentally induced hypoxia in humans causes an increase in heart rate and blood pressure with an increase in sympatho-adrenal activity.[77,78] Over time, this may lead to sustained hypertension, heart failure and a heightened sympathetic activation during the day, resulting in autonomic dysfunction.[79,80] Plasma and urine levels of catecholamines are increased in OSAS and decreased after tracheotomy.[81] Endothelial dysfunction, commonly reported in OSAS, is thought to be secondary to hypoxia-mediated changes.[82] OSAS affects endothelium through oxidative stress, inflammation, atherosclerosis and a decrease in NO.[16,83] NO is synthesized in an oxygen-dependent process[15] and responds positively to CPAP therapy in OSAS.[84] Kato *et al.* demonstrated attenuation of endothelium-dependent dilation of resistance vessels in the presence of OSAS without other co-morbidities.[15] The production of endothelin-1, a powerful vasoconstrictor, is upregulated in both OSAS and in NTG, further disrupting normal vascular regulation.[76,82,85] These results indicate an effect of OSAS on vascular regulation, loosely linking OSAS and glaucoma through an autonomic dysfunction construct.

Ischaemia

Chronic ischaemic conditions, such as atherosclerosis, have not been shown to be risk factors for glaucomatous damage.[3] Although the severity of hypoxia in OSAS is a good predictor of carotid wall thickness and plaque occurrence,[86] carotid vessel disease is not associated with glaucoma.[3] However, in NTG, there are reports showing an increase in cerebral infarcts, including an increase in silent cerebral infarcts as a marker for glaucoma progression.[87] Silent cerebral infarcts are reported in up to 30% of NTG patients, which is higher than the expected 10–11% seen in patients of similar age.[88,89] Kaiser *et al.*, through continuous electrocardiographic monitoring, showed at least one episode of silent ischaemia in 46% NTG patients (10/22) and 26% POAG patients (7/27), which was higher than that of 5% in a control group (1/20).[90] Similarly in OSAS, patients are at increased risk of stroke that is independent of hypertension and have increased white matter changes and silent infarcts.[91]

Although chronic ischaemic conditions may not be associated with glaucoma, evidence in NTG suggests an association with vasospasm-mediated ischaemia. Notably, migraines were also found to be an independent risk factor for progression in the Collaborative Normal Tension Glaucoma Study.[92] Migraines are considered episodic vasospastic events, presumably resulting in episodic alterations in blood flow. Hypoxia in OSAS is episodic in nature with subequent reperfusion, potentially creating episodic ischaemia around the nerve and endothelial dysfunction over time.

In addition, hypoxia has also been shown to stimulate platelet activation and aggregation in patients with chronic lung disease.[93,94] Increased platelet activation and aggregation were reported in OSAS, improving with CPAP therapy.[93,95] Similarly, glaucoma has also been linked to a hypercoaguable state.[96,97] Intermittent hypoxia, in addition to direct ischaemic injury and damage to endothelium, may further affect blood flow through hypercoagulation.

Inflammation and oxidative stress

Episodic hypoxia and subsequent reperfusion in OSAS can result in inflammation and oxidative stress. Oxidative by-products are increased in OSAS and are decreased with CPAP therapy.[16,98–100] Elevated markers of oxidative stress in OSAS include xanthine oxidase and lipid peroxides in the setting of a decrease in antioxidant capacity.[79] Inflammatory markers, including tumor necrosis factor-alpha (TNF-alpha) and Nuclear Factor-KappaB (NF-kB), are also

elevated in OSAS. These markers tend to decrease with CPAP therapy.[79,101]

Recently, Liu *et al*.[102] showed that a short-term elevation in IOP increases oxidative stress, leading to RGC death. Pressure-induced oxidative stress results in neuronal damage in other clinical settings, such as intracranial pressure elevation in hydrocephalus, traumatic brain injury, bacterial meningitis and stroke.[102] A pathway for glaucoma development may include increased oxidative stress and inflammation, which may have the potential to be induced by non-IOP pathways. At this time, further research is needed.

Mitochondria

Low blood flow to the optic nerve can compromise mitochondrial function, leaving the nerve more susceptible to insults such as increased IOP, light damage or inflammatory products.[102] Vascular dysregulation and hypoxia in OSA could potentially set the stage for mitochondrial dysfunction and subsequent glaucoma. Further research is needed.

Hypercapnia

A hypercapnia-mediated loss of contrast sensitivity in glaucoma patients has been suggested.[103] The cerebral and ophthalmic response to hypercapnia is complicated and somewhat difficult to measure. In general, during apnoea, there is peripheral vasoconstriction and subsequent regional vasodilation of the cerebral and myocardial circulation.[25,103] Thus, one may expect an improvement in optic nerve circulation. However, vascular regulation is more complex, because the subsequent post-apnoeic hyperventilation results in peripheral vasodilation due to relative hypocapnea.[25,103] Autonomic dysfunction could create a relative inability of ophthalmic vessels in glaucomatous eyes to dilate in glaucomatous ophthalmic vessels, resulting in a 'steal phenomenon' to the other cerebral vessels.[3,104,105] Additionally, hypercapnea increases intracranial pressure (ICP), which can change the mechanical balance at the level of the lamina cribrosa. Hypercapnea also increases metabolic stress and acidosis, potentially creating a poor circulatory environment around the optic nerve head.[3,104] Hypercapnia in OSAS as a link to glaucoma needs further research.

Conclusion

Increasing evidence suggests a strong association between glaucoma and OSAS. Surrogate markers for glaucoma, including RNFL thickness and VF mean deviation, have correlated with OSAS, AHI and oxygen saturation in reports. IOP-independent mechanisms stemming from episodic hypoxia may be the link between OSAS and glaucoma. These include perfusion pressure, autonomic dysfunction, ischaemia, inflammation, oxidative stress, mitochondrial dysfunction and hypercapnea. These mechanisms are evident in other ocular conditions associated with OSAS, such as floppy eyelid syndrome and NAION. The findings reviewed should increase the awareness of OSAS as a potential modifiable mechanism in addition to IOP for the development and progression of glaucoma.

Future studies based upon precise definitions and findings are needed to verify an association between OSAS and glaucoma. Correlation of findings needs to be made with the severity of the sleep apnoea and the presence and severity of other associated conditions, such as metabolic syndrome. Does a nocturnal blood pressure overdipper with OSAS, a nocturnal IOP rise, and a low cerebrospinal fluid pressure represent a special high-risk category? Is there an association between central sleep apnoea and glaucoma or other ocular conditions? Finally, is CPAP beneficial in slowing the progression of glaucoma in those patients who have OSAS and glaucoma? These and other studies offer a potentially fruitful area of investigation.

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